▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – PEMAZYRE® (PEMIGATINIB) TABLETS

1 NAME OF THE MEDICINE

Pemigatinib

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

PEMAZYRE 4.5 mg tablets
Each tablet contains 4.5 mg of pemigatinib.

PEMAZYRE 9 mg tablets
Each tablet contains 9 mg of pemigatinib.

PEMAZYRE 13.5 mg tablets
Each tablet contains 13.5 mg of pemigatinib.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Tablet (immediate release, uncoated).

PEMAZYRE 4.5 mg tablets
Round (5.8 mm), white to off-white tablet debossed on one side with "I" and "4.5" on the reverse.

PEMAZYRE 9 mg tablets
Oval (10 × 5 mm), white to off-white tablet debossed on one side with "I" and "9" on the reverse.

PEMAZYRE 13.5 mg tablets
Round (8.5 mm), white to off-white tablet debossed on one side with "I" and "13.5" on the reverse.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Pemigatinib has **provisional approval** in Australia for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement that has progressed after at least one prior line of systemic therapy. The decision to approve this indication has been made on the basis of overall response

rate (ORR) and duration of response (DOR). Continued approval of this indication depends on verification and description of benefit in confirmatory trial(s).

4.2 DOSE AND METHOD OF ADMINISTRATION

Therapy should be initiated by a physician experienced in the diagnosis and treatment of patients with biliary tract cancer.

FGFR2 fusion positivity status must be known prior to initiation of PEMAZYRE therapy. Assessment for FGFR2 fusion positivity in tumour specimen should be performed with an appropriate diagnostic test.

Dosage

The recommended dose is 13.5 mg PEMAZYRE taken once daily for 14 days followed by 7 days off therapy.

If a dose of PEMAZYRE is missed by 4 or more hours or vomiting occurs after taking a dose, an additional dose should not be administered and dosing should be resumed with the next scheduled dose.

Treatment should be continued as long as the patient does not show evidence of disease progression or unacceptable toxicity.

Method of administration

PEMAZYRE is for oral use. The tablets should be taken at approximately the same time every day. Patients should not crush, chew, split or dissolve the tablets. PEMAZYRE may be taken with or without food.

In all patients, a low-phosphate diet should be initiated when serum phosphate level is > 5.5 mg/dL and adding a phosphate-lowering therapy should be considered when level is > 7 mg/dL. The dose of phosphate-lowering therapy should be adjusted until serum phosphate level returns to < 7 mg/dL. Prolonged hyperphosphataemia can cause precipitation of calcium-phosphate crystals that can lead to hypocalcaemia, soft tissue mineralisation, muscle cramps, seizure activity, QT interval prolongation, and arrhythmias (see Section 4.4 Special warnings and precautions for use).

Discontinuing phosphate-lowering therapy and diet should be considered during PEMAZYRE treatment breaks or if serum phosphate level falls below normal range. Severe hypophosphataemia may present with confusion, seizures, focal neurologic findings, heart failure, respiratory failure, muscle weakness, rhabdomyolysis, and haemolytic anaemia (see Section 4.4 Special warnings and precautions for use).

Dose adjustment due to drug interaction

Concomitant use of PEMAZYRE with strong or moderate CYP3A4 inhibitors
If co-administration with a strong or moderate CYP3A4 inhibitor is necessary, the dose of patients who are taking 13.5 mg PEMAZYRE once daily should be reduced to 9 mg once daily and the dose of patients who are taking 9 mg PEMAZYRE once daily should be reduced to 4.5 mg

once daily (see Sections 4.4 Special warnings and precautions for use and 4.5 Interactions with other medicines and other forms of interactions).

Management of toxicities

Dose modifications or interruption of dosing should be considered for the management of toxicities.

PEMAZYRE dose reductions levels are summarised in Table 1.

Table 1: Recommended PEMAZYRE dose reduction levels

Dose	Dose reduction levels	
	First	Second
13.5 mg taken orally once daily for 14 days followed by 7 days off therapy	9 mg taken orally once daily for 14 days followed by 7 days off therapy	4.5 mg taken orally once daily for 14 days followed by 7 days off therapy

Treatment should be permanently discontinued if patient is unable to tolerate 4.5 mg PEMAZYRE once daily.

Dose modifications for hyperphosphataemia are provided in Table 2.

Table 2: Dose modifications for hyperphosphataemia

Adverse reaction	PEMAZYRE dose modification
> 5.5 mg/dL - ≤ 7 mg/dL	• PEMAZYRE should be continued at current dose.
> 7 mg/dL - ≤ 10 mg/dL	• PEMAZYRE should be continued at current dose, phosphate-lowering therapy should be initiated, serum phosphate should be monitored weekly, dose of phosphate lowering therapy should be adjusted as needed until level returns to < 7 mg/dL. • PEMAZYRE should be withheld if levels do not return to < 7 mg/dL within 2 weeks of starting a phosphate lowering therapy. PEMAZYRE and phosphate-lowering therapy should be restarted at the same dose when level returns to < 7 mg/dL. • Upon recurrence of serum phosphate at > 7 mg/dL with phosphate-lowering therapy, PEMAZYRE should be reduced 1 dose level.
> 10 mg/dL	• PEMAZYRE should be continued at current dose, phosphate-lowering therapy should be initiated, serum phosphate should be monitored weekly and dose of phosphate lowering therapy should be adjusted as needed until level returns to < 7 mg/dL. • PEMAZYRE should be withheld if levels continue > 10 mg/dL for 1 week. PEMAZYRE and phosphate-lowering therapy should be restarted 1 dose level lower when serum phosphate is < 7 mg/dL. • If there is recurrence of serum phosphate > 10 mg/dL following 2 dose reductions, PEMAZYRE should be permanently discontinued.

Dose modifications for serous retinal detachment are provided in Table 3.

Table 3: Dose modifications for serous retinal detachment

Adverse reaction	PEMAZYRE dose modification
Asymptomatic	• PEMAZYRE should be continued at current dose. Monitoring should be performed as described in Section 4.4 Special warnings and precautions for use.
Moderate decrease in visual acuity (best corrected visual acuity 20/40 or better or ≤ 3 lines of decreased vision from baseline); limiting instrumental activities of daily living	• PEMAZYRE should be withheld until resolution. If improved on subsequent examination, PEMAZYRE should be resumed at the next lower dose level. • If it recurs, symptoms persist or examination does not improve, permanent discontinuation of PEMAZYRE should be considered based on clinical status.
Marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or > 3 lines decreased vision from baseline up to 20/200); limiting activities of daily living	• PEMAZYRE should be withheld until resolution. If improved on subsequent examination, PEMAZYRE may be resumed at 2 dose levels lower. • If it recurs, symptoms persist or examination does not improve, permanent discontinuation of PEMAZYRE should be considered, based on clinical status.
Visual acuity worse than 20/200 in affected eye; limiting activities of daily living	• PEMAZYRE should be withheld until resolution. If improved on subsequent examination, PEMAZYRE may be resumed at 2 dose levels lower. • If it recurs, symptoms persist or examination does not improve, permanent discontinuation of PEMAZYRE should be considered, based on clinical status.

Special populations

Elderly patients
The dose of PEMAZYRE is the same in elderly patients as younger adult patients (see Section 5.1 Pharmacodynamic properties).

Renal impairment
Dose adjustment is not required for patients with mild, moderate renal impairment or End Stage Renal Disease (ESRD) on haemodialysis. For patients with severe renal impairment, the dose of patients who are taking 13.5 mg PEMAZYRE once daily should be reduced to 9 mg once daily and the dose of patients who are taking 9 mg PEMAZYRE once daily should be reduced to 4.5 mg once daily (see Section 5.2 Pharmacokinetic properties).

Hepatic impairment
Dose adjustment is not required for patients with mild or moderate hepatic impairment. For patients with severe hepatic impairment, the dose of patients who are taking 13.5 mg

PEMAZYRE once daily should be reduced to 9 mg once daily and the dose of patients who are taking 9 mg PEMAZYRE once daily should be reduced to 4.5 mg once daily (see Section 5.2 Pharmacokinetic properties).

Paediatric population
The safety and efficacy of PEMAZYRE in patients less than 18 years of age have not been established. No data are available.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1 List of excipients.

Concomitant use with St John's wort (see Section 4.5 Interactions with other medicines and other forms of interactions).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hyperphosphataemia

Hyperphosphataemia is a pharmacodynamic effect expected with PEMAZYRE administration (see Section 5.1 Pharmacokinetic properties). Prolonged hyperphosphataemia can cause precipitation of calcium-phosphate crystals that can lead to hypocalcaemia , soft tissue mineralisation, anaemia, secondary hyperparathyroidism, muscle cramps, seizure activity, QT interval prolongation, and arrhythmias (see Section 4.2 Dose and method of administration). Soft tissue mineralisation, including cutaneous calcification, calcinosis and non-uremic calciphylaxis have been observed with PEMAZYRE treatment.

Recommendations for management of hyperphosphataemia include dietary phosphate restriction, administration of phosphate-lowering therapy, and dose modification when required (see Section 4.2 Dose and method of administration).
Phosphate-lowering therapy was used by 28.5 % of patients during treatment with PEMAZYRE (see Section 4.8 Adverse effects (undesirable effects)).

Hypophosphataemia

Discontinuing phosphate-lowering therapy and diet should be considered during PEMAZYRE treatment breaks or if serum phosphate level falls below normal range. Severe hypophosphataemia may present with confusion, seizures, focal neurologic findings, heart failure, respiratory failure, muscle weakness, rhabdomyolysis, and haemolytic anaemia (see Section 4.2 Dose and method of administration). Hypophosphataemia reactions were ≥ Grade 3 in 12.3% of participants. None of the events were serious, led to discontinuation or to dose reduction. Dose interruption occurred in 1.4 % of participants.

For patients presenting with hyperphosphataemia or hypophosphataemia, additional close monitoring and follow-up is recommended regarding dysregulation of bone mineralisation.

Serous retinal detachment

PEMAZYRE can cause serous retinal detachment reactions, which may present with symptoms such as blurred vision, visual floaters, or photopsia (see Section 4.8 Adverse effects (undesirable effects)). This can moderately influence the ability to drive and use machines (see Section 4.7 Effects on ability to drive and use machines).

Ophthalmological examination, including optical coherence tomography (OCT) should be performed prior to initiation of therapy and every 2 months for the first 6 months of treatment, every 3 months afterwards, and urgently at any time for visual symptoms. For serous retinal detachment reactions, the dose modification guidelines should be followed (see Section 4.2 Dose and method of administration).

During the conduct of the clinical study, there was no routine monitoring, including OCT, to detect asymptomatic serous retinal detachment; therefore, the incidence of asymptomatic serous retinal detachment with PEMAZYRE is unknown.

Careful consideration should be taken with patients that have clinically significant medical eye disorders, such as retinal disorders, including but not limited to, central serous retinopathy, macular/retinal degeneration, diabetic retinopathy, and previous retinal detachment.

Dry eye

PEMAZYRE can cause dry eye (see Section 4.8 Adverse effects (undesirable effects)). Patients should use ocular demulcents, in order to prevent or treat dry eye, as needed.

Embryo-fetal toxicity

Based on the mechanism of action and findings in an animal reproduction study (see Section 5.3 Preclinical safety data), PEMAZYRE can cause fetal harm when administered to a pregnant woman. Pregnant women should be advised of the potential risk to the fetus. Women of childbearing potential should be advised to use effective contraception during treatment with pemigatinib and for 1 week after the last dose.

Male patients with female partners of childbearing potential should be advised to use effective contraception during treatment with PEMAZYRE and for at least 1 week after the last dose (see Section 4.6 Effects on fertility, pregnancy and lactation).

Blood creatinine increase

Pemigatinib may increase serum creatinine by decreasing renal tubular secretion of creatinine; this may occur due to inhibition of renal transporters OCT2 and MATE1 and may not affect glomerular function. Within the first cycle, serum creatinine increased (mean increase of 0.2 mg/dL) and reached steady state by Day 8, and then decreased during the 7 days off therapy (see Section 4.8 Adverse effects (undesirable effects)). Alternative markers of renal function should be considered if persistent elevations in serum creatinine are observed.

Combination with strong and moderate CYP3A4 inhibitors

Concomitant use of PEMAZYRE with strong and moderate CYP3A4 inhibitors requires dose adjustment (see Sections 4.2 Dose and method of administration and 4.5 Interactions with other medicines and other forms of interactions).

Combination with strong or moderate CYP3A4 inducers

Concomitant use of PEMAZYRE with strong or moderate CYP3A4 inducers is not recommended (see Section 4.5 Interactions with other medicines and other forms of interactions).

Contraception

Based on findings in an animal study and its mechanism of action, PEMAZYRE can cause fetal harm when administered to a pregnant woman. Women of childbearing age being treated with PEMAZYRE should be advised not to become pregnant and men being treated with PEMAZYRE

should be advised not to father a child during treatment. An effective method of contraception should be used in women of childbearing potential and in men with women partners of childbearing potential during treatment with PEMAZYRE and for 1 week following completion of therapy (see Section 4.6 Fertility, pregnancy and lactation).

Pregnancy test

A pregnancy test should be performed before treatment initiation to exclude pregnancy.

Use In the elderly

Refer to Section 4.2 Dose and Method of Administration and Section 5.1 Clinical trials.

Paediatric use

The safety and efficacy of PEMAZYRE in patients less than 18 years of age has not been established. No data is available.

Effects on laboratory tests

See Section 4.8 Adverse effects (undesirable effects).

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Effects of other medicinal products on PEMAZYRE

Strong and Moderate CYP3A4 inhibitors

A strong CYP3A4 inhibitor (itraconazole 200 mg once daily) increased pemigatinib AUC geometric mean by 88 % (90 % CI of 75 %, 103 %), which may increase the incidence and severity of adverse reactions with PEMAZYRE.

Concomitant use of a strong or moderate CYP3A4 inhibitor with PEMAZYRE increases pemigatinib plasma concentrations, which may increase incidence and severity of adverse reactions. Avoid concomitant use of strong and moderate CYP3A4 inhibitors with PEMAZYRE. Reduce PEMAZYRE dosage if concomitant use of strong and moderate CYP3A4 inhibitors cannot be avoided.

Patients who are taking 13.5 mg PEMAZYRE once daily should have their dose reduced to 9 mg once daily and patients who are taking 9 mg PEMAZYRE once daily should have their dose reduced to 4.5 mg once daily (see Section 4.2 Dose and method of administration).

Strong and Moderate CYP3A4 Inducers

A strong CYP3A4 inducer (rifampicin 600 mg once daily) decreased pemigatinib AUC geometric mean by 85 % (90 % CI of 84 %, 86 %), which may decrease the efficacy of PEMAZYRE.

Concomitant use of PEMAZYRE with a strong or moderate CYP3A4 inducer decreases plasma concentrations, which may reduce the efficacy of PEMAZYRE. Avoid concomitant use of strong and moderate CYP3A4 inducers with PEMAZYRE.

Concurrent use of strong CYP3A4 inducers (e.g. carbamazepine, phenytoin, phenobarbital, rifampicin) should be avoided during treatment with PEMAZYRE (see Section 4.4 Special warnings and precautions for use).

Concomitant use of PEMAZYRE with St John's wort is contraindicated (see Section 4.3 Contraindications*).* If needed, other enzyme inducers (e.g. efavirenz) should be used under close surveillance.

Proton pump inhibitors
Pemigatinib geometric mean ratios (90 % CI) for C_{max} and AUC were 65.3 % (54.7, 78.0) and 92.1 % (88.6, 95.8), respectively, when co-administered in healthy subjects with esomeprazole (a PPI) relative to pemigatinib alone. Co-administration of a proton pump inhibitor (esomeprazole) did not result in a clinically important change in pemigatinib exposure.

However, in more than one third of patients given PPIs, a significant reduction of the exposure of pemigatinib was observed. PPIs should be avoided in patients receiving pemigatinib.

H2-receptors antagonists
Co-administration of ranitidine did not result in a clinically important change in pemigatinib exposure.

Effects of pemigatinib on other medicinal products

Effect of pemigatinib on CYP2B6 substrates
In vitro studies indicate that pemigatinib induces CYP2B6. Co-administration of pemigatinib with CYP2B6 substrates (e.g. cyclophosphamide, ifosfamide, methadone, efavirenz) may decrease their exposure. Close clinical surveillance is recommended when PEMAZYRE is administered with these medicinal products.

Effect of pemigatinib on P-gp substrates
In vitro, pemigatinib is an inhibitor of P-gp. Co-administration of PEMAZYRE with P-gp substrates (e.g. digoxin, dabigatran, colchicine) may increase their exposure and thus their toxicity. PEMAZYRE administration should be separated by at least 6 hours before or after administration of P-gp substrates with a narrow therapeutic index.

CYP substrates
Pemigatinib at clinically relevant concentrations is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 or an inducer of CYP1A2, CYP2B6 and CYP3A4.

Transporters
Pemigatinib is a substrate of both P-gp and BCRP. P-gp or BCRP inhibitors are not expected to affect pemigatinib exposure at clinically relevant concentrations. *In vitro*, pemigatinib is an inhibitor of OATP1B3, OCT2, and MATE1. Inhibition of OCT2 may increase serum creatinine.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no data on the impact of PEMAZYRE on human fertility. Animal fertility studies have not been conducted with pemigatinib . In repeated dose toxicity studies, oral administration of pemigatinib did not result in any dose-related adverse effects on male and female reproductive

organs. Based on the pharmacology of pemigatinib, impairment of male and female fertility cannot be excluded.

Use in pregnancy – Pregnancy Category D

There are no available data from the use of PEMAZYRE in pregnant women. An embryofetal developmental study in rats has shown reproductive toxicity. Once daily oral administration of pemigatinib during the period of organogenesis resulted in 100 % post implantation loss at doses ≥ 0.3 mg/kg (approximately 0.3 times the human exposure based on AUC at the clinical dose of 13.5 mg). Fetal survival was not affected at 0.1 mg/kg/day; however, once daily oral administration of pemigatinib at the 0.1 mg/kg dose level (approximately 0.1 times the human exposure based on AUC at the clinical dose of 13.5 mg) resulted in an increase in fetal skeletal and visceral malformations, major blood vessels variations, reduced ossification and decrease fetal body weight.

Based on animal data and pharmacology of pemigatinib, PEMAZYRE should not be used during pregnancy unless the clinical condition of the women requires treatment with PEMAZYRE. A pregnancy test should be performed before treatment initiation to exclude pregnancy.

Contraception in men and women/women of childbearing potential

Based on findings in an animal study and its mechanism of action, pemigatinib can cause fetal harm when administered to a pregnant woman. Women of childbearing potential being treated with PEMAZYRE should be advised not to become pregnant and men being treated with PEMAZYRE should be advised not to father a child during treatment. An effective method of contraception should be used in women of childbearing potential and in men with women partners of childbearing potential during treatment with PEMAZYRE and for 1 week following completion of therapy. Since the effect of PEMAZYRE on the metabolism and efficacy of contraceptives has not been investigated, barrier methods should be applied as a second form of contraception, to avoid pregnancy.

Use in lactation

There are no data on whether pemigatinib or its metabolites are excreted in human milk. A risk to the breast-fed child cannot be excluded. Breast-feeding should be discontinued during treatment with PEMAZYRE and for 1 week following completion of therapy.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Adverse reactions such as fatigue and visual disturbances have been associated with PEMAZYRE. Therefore, caution should be recommended when driving or operating machines (see Section 4.4 Special warnings and precautions for use).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

The safety of PEMAZYRE was evaluated in Study 1 (FIGHT-202), which included 147 patients with previously treated, advanced, or metastatic cholangiocarcinoma. Patients were treated with PEMAZYRE in 21-day cycles consisting of 13.5 mg oral dosing once daily for 14 days on / 7 days off therapy.

The most common adverse reactions were hyperphosphataemia; includes hyperphosphataemia and blood phosphorous increased (60.5%), alopecia (49.7%), diarrhoea (46.9%), nail toxicity (44.9%), fatigue (43.5%), nausea (41.5%), dysgeusia (40.8%), stomatitis (37.4%), constipation (36.7%), dry mouth (34.0%), dry eye (27.9%), arthralgia (25.9%), hypophosphataemia (23.1%), dry skin (21.8%) and palmar-plantar erythrodysaesthesia syndrome (16.3%).

The most common serious adverse reactions were hyponatremia (2.1 %) and blood creatinine increase (1.4 %) and fatigue (1.4 %). No serious adverse reaction led to PEMAZYRE dose reduction. One serious adverse reaction of hyponatremia (0.7 %) led to dose interruption. One serious adverse reaction of blood creatinine increase (0.7 %) led to dose discontinuation.

A serious eye disorder adverse reaction of retinal detachment (0.7 %) was observed. Non-arteritic optic ischemic neuropathy (0.7 %) and retinal artery occlusion (0.7 %) were observed and are considered adverse events.

Table 4: Summary of Treatment-Emergent Adverse Events Occurring in ≥ 15% of Participants Overall (all cohorts) by MedDRA Preferred Term (Safety Population) in FIGHT-202

	Total (All Cohorts) (N = 147)	
MedDRA Preferred Term, n (%)	**All Grades**	**≥ Grade 3**
Hyperphosphataemia	86 (58.5)	0
Alopecia	73 (49.7)	0
Diarrhoea	69 (46.9)	5 (3.4)
Fatigue	64 (43.5)	8 (5.4)
Nausea	61 (41.5)	3 (2.0)
Dysgeusia	60 (40.8)	0
Stomatitis	55 (37.4)	9 (6.1)
Constipation	54 (36.7)	1 (0.7)
Decreased appetite	50 (34.0)	3 (2.0)
Dry mouth	50 (34.0)	0
Vomiting	43 (29.3)	2 (1.4)
Dry eye	41 (27.9)	1 (0.7)
Arthralgia	38 (25.9)	9 (6.1)
Abdominal pain	34 (23.1)	8 (5.4)
Hypophosphataemia	34 (23.1)	21 (14.3)
Dry skin	32 (21.8)	1 (0.7)
Back pain	31 (21.1)	4 (2.7)
Pain in extremity	29 (19.7)	3 (2.0)
Oedema peripheral	26 (17.7)	1 (0.7)
Urinary tract infection	26 (17.7)	4 (2.7)

MedDRA Preferred Term, n (%)	Total (All Cohorts) (N = 147)	
	All Grades	≥ Grade 3
Weight decreased	26 (17.7)	3 (2.0)
Palmar-plantar erythrodysaesthesia syndrome	24 (16.3)	7 (4.8)
Headache	23 (15.6)	0
Hypercalcaemia	23 (15.6)	3 (2.0)
Dehydration	22 (15.0)	5 (3.4)
Pyrexia	22 (15.0)	1 (0.7)

Tabulated list of adverse reactions

Adverse reactions reported in all cholangiocarcinoma patients are presented in Table 5. Frequency categories are very common (≥ 1/10), common (≥ 1/100 to < 1/10) and uncommon (≥ 1/1,000 to < 1/100). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 5: Adverse reactions observed in FIGHT-202 study – frequency reported by incidence of treatment emergent events

System organ class	Frequency	Adverse reactions
Metabolism and nutrition disorders	Very common	Hyponatraemia, Hyperphosphataemia[a], Hypophosphataemia[b]
Nervous system disorders	Very common	Dysgeusia
Eye disorders	Very common	Dry eye
	Common	Serous retinal detachment[c], Punctate keratitis, Vision blurred, Trichiasis
	Uncommon	Photopsia
Gastrointestinal disorders	Very common	Nausea, Stomatitis, Diarrhoea, Constipation, Dry mouth
Skin and subcutaneous tissue disorders	Very common	Palmar-plantar erythrodysaesthesia syndrome, Nail toxicity[d], Alopecia, Dry skin
	Common	Hair growth abnormal
Musculoskeletal and connective tissue disorders	Very common	Arthralgia
General disorders and administration site conditions	Very common	Fatigue
Investigations	Very common	Blood creatinine increased

[a] Includes Hyperphosphataemia and Blood phosphorous increased
[b] Includes Hypophosphataemia and Blood phosphorous decreased
[c] Includes Serous retinal detachment, Retinal detachment, Detachment of retinal pigmented epithelium, Retinal thickening, Subretinal fluid, Chorioretinal folds, Chorioretinal scar, and Maculopathy.

[d] Includes Nail toxicity, Nail disorder, Nail discolouration, Nail dystrophy, Nail hypertrophy, Nail ridging, Nail infection, Onychalgia, Onychoclasis, Onycholysis, Onychomadesis, Onychomycosis and Paronychia

Description of selected adverse reactions

Hyperphosphataemia
Hyperphosphataemia (including increased blood phosphorous) was reported in 60.5 % of all patients treated with PEMAZYRE. Hyperphosphataemia above 7 mg/dL and 10 mg/dL was experienced by 27% and 0% of patients, respectively. Hyperphosphataemia usually develops within the first 15 days.

None of the reactions were ≥ Grade 3 in severity, or led to discontinuation of PEMAZYRE. Dose interruption occurred in 1.4 % patients and reduction in 0.7 % of patients. These results suggest that dietary phosphate restriction and/or administration of phosphate-lowering therapy along with the 1-week dose holiday were effective strategies for managing this on-target effect of PEMAZYRE.

Recommendations for management of hyperphosphataemia are provided in Sections 4.2 Dose and method of administration and 4.4 Special warnings and precautions for use.

Serous retinal detachment
Serous retinal detachment occurred in 4.8 % of all patients treated with PEMAZYRE. Reactions were generally Grade 1 or 2 (3.4 %) in severity; ≥ Grade 3 and serious reactions included retinal detachment in 1 patient (0.7 %). Two adverse reactions of retinal detachment (0.7 %) and detachment of retinal pigment epithelium (0.7 %) led to dose interruption. None of the reactions led to dose reduction or discontinuation.

Recommendations for management of serous retinal detachment are provided in Sections 4.2 Dose and method of administration and 4.4 Special warnings and precautions for use.

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is no information on overdose of PEMAZYRE.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Pemigatinib is a small molecule kinase inhibitor of FGFR1, 2 and 3 with IC_{50} values of less than 2 nM. Pemigatinib also inhibited FGFR4 *in vitro* at a concentration approximately 100 times higher than those that inhibit FGFR1, 2, and 3. It inhibits FGFR 1-3 phosphorylation and

signalling and decreases cell viability in cancer cells lines with activating FGFR genetic alterations, including point mutations, amplifications, and fusions or rearrangements that resulted in constitutive activation of FGFR signalling. FGFR2 fusions/rearrangements are strong oncogenic drivers and are the most common FGFR alteration occurring, almost exclusively, in 10-16 % of intrahepatic cholangiocarcinoma (CCA). Constitutive FGFR signalling can support the proliferation and survival of malignant cells. Pemigatinib exhibited anti – tumour activity in mouse xenograft models of human tumours with FGFR1, FGFR2, or FGFR3 alterations resulting in constitutive FGFR activation including a patient- derived xenograft model of cholangiocarcinoma that expressed an oncogenic FGFR2-Transformer-2 beta homolog (TRA2b) fusion protein.

Pharmacodynamic effects

Serum phosphate
Pemigatinib increased serum phosphate level as a consequence of FGFR inhibition. In pemigatinib clinical studies, phosphate-lowering therapy and dose modifications were permitted to manage hyperphosphataemia (see Sections 4.2 Dose and method of administration, 4.4 Special warnings and precautions for use and 4.8 Adverse effects (undesirable effects)).

Clinical trials

FIGHT-202 was a multicentre, open-label, single-arm study to evaluate the efficacy and safety of PEMAZYRE in previously treated patients with locally advanced/metastatic or surgically unresectable cholangiocarcinoma. The efficacy population consists of 108 patients (105 patients with intrahepatic disease) that had progressed after at least 1 prior therapy and who had FGFR2 fusion or rearrangement, as determined by the test performed at a central laboratory.

Patients received PEMAZYRE in 21-days cycles consisting of 13.5 mg once daily oral dosing for 14 days, followed by 7 days off therapy. PEMAZYRE was administered until disease progression or unacceptable toxicity. The major efficacy outcome measures were objective response rate (ORR) and duration of response (DoR), as determined by independent review committee (IRC) according to RECIST v1.1.

The median age was 56 years (range: 26 to 77 years), 31.5 % were ≥ 65 years, 60.7 % were female, and 73.8 % were Caucasian. Most (95.4 %) patients had a baseline Eastern Cooperative Oncology Group (ECOG) performance status of 0 (42.1 %) or 1 (53.3 %). All patients had at least 1 prior line of systemic therapy, 27.1 % had 2 prior lines of therapy, and 12.1 % had 3 or more prior lines of therapy. Ninety-six percent of patients had received prior platinum-based therapy including 76 % with prior gemcitabine/cisplatin.

Efficacy results are summarised in Table 6.

The median time to response was 2.7 months (range 0.7 – 6.9 months).

Table 6: Efficacy results

	Cohort A (FGFR2 fusion or rearrangement) Efficacy Evaluable Population (N = 108)
ORR (95 % CI)	37.0 % (27.94, 46.86)
Complete response (N)	3.7 % (4)
Partial response (N)	33.3 % (36)
Stable disease (N)	49 % (45.4)
Median Disease control rate (95% CI)	82.2% (73.7, 89.0)
Median progression free survival (months) (95% CI)	7.03 (6.08, 10.48)
Median Survival (months) (95% CI)	17.48 (14.42, 22.93)
Median duration of response (months) (95 % CI)[a]	8.08 (5.65, 13.14)
Kaplan-Meier estimates of duration of response (95 % CI)	
3 months	100.0 (100.0, 100.0)
6 months	66.0 (48.0, 79.1)
9 months	47.6 (30.2, 63.1)
12 months	37.5 (21.3, 53.7)

ORR- CR+PR
CI= Confidence Interval
Note: Data are from IRC per RECIST v1.1, and complete and partial responses are confirmed.
[a] The 95 % CI was calculated using the Brookmeyer and Crowley's method

Elderly patients

In the clinical study of pemigatinib, 31.5 % of patients were 65 years and older, and 7.5 % of patients were 75 years and older. No difference in efficacy response was detected between these patients and in patients < 65 years of age.

5.2 PHARMACOKINETIC PROPERTIES

Pemigatinib exhibits linear pharmacokinetics in the dose range of 1 to 20 mg. Following oral administration of PEMAZYRE 13.5 mg once daily, steady-state was reached by 4 days with a geometric mean accumulation ratio of 1.6. The geometric mean steady-state $AUC_{0\text{-}24h}$ was 2620 nM·h (54 % CV) and C_{max} was 236 nM (56 % CV) for 13.5 mg once daily.

Absorption

Median time to achieve peak plasma concentration (t_{max}) was 1 to 2 hours.

No clinically meaningful differences with pemigatinib pharmacokinetics were observed following administration of a high-fat and high-calorie meal (800 calories to 1,000 calories with approximately 50 % of total caloric content of the meal from fat) in patients with cancer.

Distribution

Pemigatinib is 90.6 % bound to human plasma proteins at concentrations ranging from 1 to 10 µM, predominantly to albumin. The estimated apparent volume of distribution was 235 L (60.8 %) in patients with cancer.

Metabolism

Pemigatinib is predominantly metabolised by CYP3A4 *in vitro*. Following oral administration of a single 13.5 mg radiolabeled pemigatinib dose, unchanged pemigatinib was the major drug-related moiety in plasma, and no metabolites >10 % of total circulating radioactivity were observed.

Elimination

Following oral administration of pemigatinib 13.5 mg once daily in patients with cancer, the geometric mean elimination half-life (t½) was 15.4 (51.6 % CV) hours and the geometric mean apparent clearance (CL/F) was 10.6 L/h (54 % CV).

Excretion

Following a single oral dose of radiolabeled pemigatinib, 82.4 % of the dose was recovered in feces (1.4 % as unchanged) and 12.6 % in urine (1 % as unchanged).

Renal impairment

The effect of renal impairment on the pharmacokinetics of pemigatinib was evaluated in a renal impairment study in subjects with normal renal function (GFR ≥ 90 mL/min), severe renal function (GFR < 30 mL/min and not on haemodialysis) and End Stage Renal Disease (ESRD) (GFR < 30 mL/min and on haemodialysis). In subjects with the severe renal impairment, the geometric mean ratios (90% CI) compared to normal controls were 64.6 % (44.1 %, 94.4 %) for C_{max} and 159 % (95.4 %, 264 %) for $AUC_{0-\infty}$. In the subjects with ESRD before haemodialysis, the geometric mean ratios (90 % CI) was 77.5 % (51.2 %, 118 %) for C_{max} and 76.8 % (54.0 %, 109 %) for $AUC_{0-\infty}$. Besides, in participants with ESRD after haemodialysis, the geometric mean ratios (90 % CI) were 90.0 % (59.3 %, 137 %) for C_{max} and 91.3 % (64.1 %, 130 %) for $AUC_{0-\infty}$. Based on these results, PEMAZYRE dose should be reduced for patients with severe renal impairment (see Section 4.2 Dose and method of administration).

Hepatic impairment

The effect of hepatic impairment on the pharmacokinetics of pemigatinib was evaluated in a hepatic impairment study in subjects with normal hepatic function, moderate (Child-Pugh class B) and severe (Child-Pugh class C) hepatic impairment. In subjects with moderate hepatic impairment, the geometric mean ratios (90 % CI) compared to normal controls, were 96.7 % (59.4 %, 157 %) for C_{max} and 146 % (100 %, 212 %) for $AUC_{0-\infty}$. In subjects with severe hepatic impairment, the GMR (90 % CI) was 94.2 % (68.9 %, 129 %) for C_{max} and 174 % (116 %, 261 %)

for $AUC_{0-\infty}$. Based on these results, no dose adjustment is recommended for patients with mild and moderate hepatic impairment. However, PEMAZYRE dose should be reduced for patients with severe hepatic impairment (see Section 4.2 Dose and method of administration).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Pemigatinib was not mutagenic in a bacterial mutagenicity assay, nor clastogenic in an *in vitro* chromosome aberration assay, and did not result in induction of bone marrow micronuclei in an *in vivo* micronucleus assay in rats.

Carcinogenicity

Carcinogenicity studies with pemigatinib have not been conducted.

Systemic toxicity

The most prominent findings following repeat-dose oral administration of pemigatinib in both rats and monkeys were attributed to the intended pharmacology of pemigatinib (FGFR1, FGFR2, and FGFR3 inhibition), including hyperphosphataemia, physeal dysplasia, and soft tissue mineralisation; the findings were observed at exposure levels (AUC) less than at the human exposure at the recommended clinical dose of 13.5 mg. Mineralisation was observed in numerous tissues including kidneys, stomach, arteries, ovaries (monkey only), and eyes (cornea, rat only). Soft tissue mineralisation was not reversible, while physeal and cartilage findings were reversible. In addition, changes of the bone marrow (rats) and kidney lesions were observed.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Microcrystalline cellulose
Sodium starch glycollate (Type A)
Magnesium stearate

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

ACLAR/PVC/Al blister containing 14 tablets. Carton box containing 14 or 28 tablets.

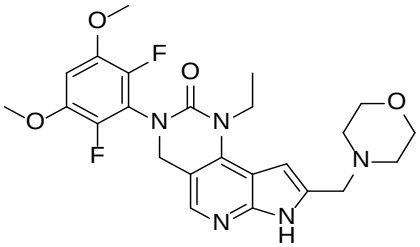
Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



Chemical name: 3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-8-(morpholin-4-ylmethyl)-1,3,4,7-tetrahydro-2*H*-pyrrolo[3',2':5,6]pyrido[4,3-*d*]pyrimidin-2-one

Molecular Formula: $C_{24}H_{27}F_2N_5O_4$

Molecular Weight: 487.5 g/mole

CAS number

1513857-77-6

7 MEDICINE SCHEDULE (POISONS STANDARD)

PRESCRIPTION ONLY MEDICINE (S4)

8 SPONSOR

Specialised Therapeutics Alim Pty Ltd
Level 2, 17 Cotham Road, Kew, Victoria 3101

Ph: 1300 798 820
Fax: 1800 798 829

www.stbiopharma.com

9 DATE OF FIRST APPROVAL

12 September 2022

Attachment 1: Product information for AusPAR - Pemazyre - pemigatinib - Specialised Therapeutics Alim Pty Ltd - PM-2021-03777-1-4 Final 3 July 2023. This is the Product Information that was approved with the submission described in this AusPAR. It may have been superseded. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/products/australian-register-therapeutic-goods-artg/product-information-one>

10 DATE OF REVISION

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information